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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,769	12/09/2003	Robert A. Kirken	2105-00401	4261

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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,769	KIRKEN ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *9,13-30,32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-12 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05/09/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election, without traverse, with the Group I(a), which is directed to a method of inhibiting function and/or proliferation of a cell expressing Janus tyrosine kinase 3 with administering a compound represented by the formula I, is acknowledged.

2. It is noted that claims 29 and 30 were inadvertently included in the Group I(a) invention. As explained in the pages 3-4 of the O.A. mailed 03/15/06, claims 29 and 30 were separately included in Group I(b) and Group I(c) invention due to their different classification. Accordingly, claims 29 and 30 are not included in the Group I(a) invention, and claims 9, 13-30 and 32-33 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims.

3. Claims 1-8, 10-12 and 31 are currently pending for prosecution on the merits.

Information Disclosure Statement

4. Acknowledgement is made of applicant's submitting of the information disclosure statement (IDS) on May 09, 2005. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement (IDS) has been considered by the examiner.

5. With respect to "PCT International Search Report, PCT/US03/38993" in the submitted PTO-1449, the information disclosure statement filed May 09, 2005 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office.

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-8, 10-12 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing proliferation of a cell expressing Janus tyrosine kinase 3 or suppressing an undesired function of a cell expressing Janus tyrosine kinase 3 with compound represented by the formula I or a salt thereof, does not reasonably provide enablement for "inhibiting function and/or proliferation of a cell expressing Janus tyrosine kinase 3" or "suppressing an undesired function of a cell expressing Janus tyrosine kinase 3" with "a metabolite" or "a precursor". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d

1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant claims are drawn to a method for inhibiting (The American Heritage Dictionary, Second Edition, 1982, defines "inhibit" as "to restraint or hold back; prevent; to prohibit; fobid") function and/or proliferation of a cell expressing Janus tyrosine kinase 3 by administering a compound of the formula I or salt thereof or in vivo method of suppressing an undesired function of a cell expressing Janus tyrosine kinase 3 by administering a compound of the formula I or salt thereof or a metabolite or a precursor.

The claimed compounds (mannich bases of alicyclic ketones) are known in the art as fungistatic agent, choloretic agent or cytotoxic agent (Qi et al., Yingyong Huaxue, 2002, 19(3), 243-246; Dimmock et al., Pharmazie, 1995, 50(1), 668-71; Dimmock et al., European Journal of Medicinal Chemistry, 1993, 28(4), 313-22; FR 1466205 or CA 712187; DE 1138763; FR M100).

With respect to the scope of enable for "inhibition",

There are no known compounds of similar structure which have been demonstrated to inhibit (prevention, complete eradication or total inhibition) of function and proliferation of a cell

expressiong Janus tyrosine kinase 3. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits.

The relative skill of those in the art of pharmaceuticals and unpredictability of the pharmaceutical art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The instant claims embrace the preventive measure or total inhibition of the claimed underlying mechanism achieved by the administration of the claimed plethora of compounds that are represented by compound of Formula I, a pharmaceutically acceptable salt, a metabolite or precursor.

The specification provides assay method (in vitro) in using compound 649641P, and disclosed that said compound is effective in reducing the proliferation of γc/Jak3-dependent PHA-activated human T-cells or proliferation of T-cells culture in the presence of the Jak2 activator or the Jak3 activator. However, there is no demonstrated correlation that tests and results apply to the claimed preventive utility (total inhibition) embraced by the instant claims.

Since the efficacy of said compound in preventing or completely inhibiting the claimed mechanism cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary

skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

With respect to the scope of enablement for "a metabolite" or "a precursor",

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5(BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 9999 F.2d 1577, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990).

The claims are very broad due to the vast number of possible compounds of that are described as being "a metabolite" or "a precursor".

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fishcher, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of the physiological or pharmaceutical activity of "a metabolite" or "a precursor" is insufficient for enablement. The specification provides no guidance, in the way of enablement for "a metabolite" or "a precursor" other compound of the formula or its salt. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreschfiedl, 110 F. 2d 235, 45 USPQ 36 (CCPA 1940), vies this general rule: "it is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the

members of a group or by other appropriate language, that the chemicals or chemical combination included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S.5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

As stated above, the specification discloses a compound of the formula I or its salt, and tested 649641P in vitro or vivo and fount that said compound is effective in reducing the proliferation of γc/Jak3-dependent PHA-activated human T-cells, proliferation of T-cells culture in the presence of the Jak2 activator or the Jak3 activator and allograft survival. However, the instant specification does not provide sufficient guidance in how to make/use "a metabolite" or "a precursor". The skill artisan would have not known that which compounds of the claimed compounds are capable of accomplishing the desired result of the claimed invention **without undue amount of experimentation**.

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the

art would be burdened with undue "painstaking experimentation study" to determine all of "a metabolite" or "a precursor" that would be enabled in this specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 6, 12 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 12 recite "at least once compound is substantially non-inhibitory or protein tyrosine kinase activity other than Janus tyrosine 3 activity" and "continuously or periodically administering said pharmaceutical composition to the subject" respectively. The term "substantially", "continuously" or "periodically" in claims 6 and 12 respectively is a relative term which renders the claim indefinite. The term "substantially", "continuously" or "periodically" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 31 recites "at least one compound of the formula". Accordingly to the formula structure in claim 31, there is only one compound such as 2,12-bis[(dimethylamino)methyl]cyclododecanone possible. However, the recitation of "at least one compound of the formula" allows for the inclusion of more than one compound derived from the formula structure. This inconsistency leaves the reader in doubt as to the meaning of the

invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-6, 8 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Dimmock et al. (Pharmazie, 1995, 50(1), 668-71).

Dimmock teaches a compound of the formula in claim 31 (2,12-bis[(dimethylamino)methyl]cyclododecanone or its hydrochloride salt) as a cytotoxic agent that was tested in vitro against murine P388 D1 lyphocytic leukemia cells.

Although Dimmock is silent about the activity of said compound in "inhibiting function and/or proliferation of a cell expressing Janus tyrosine kinase 3" (claims 1-6, 8 and 31), "cell division is blocked" (claim 5), "substantially non-inhibitory of protein tyrosine kinase activity other than Janus tyrosine kinase 3 activity" (claim 6) and " less capable of inhibiting Jak2 and Stat5a/b activation by prolactin (PRL) at a concentration sufficient to inhibit Jak3 and Stat5a/b activated by IL2" (claim 8), such characteristic or property must be inherent to the referenced teaching since the administration of same compound in overlapping dosage amount (see Table 1 of Dimmock and Example 1 of the instant specification) to the claimed lymphoid origin cell

would inherently provide the claimed utility. Thus, the reference anticipates the claimed invention.

10. Claims 1, 4, 5, 6, 7, 8 and 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Chimie et Atomistique (FR 1466205 or CA 712187).

FR 1466205 teaches use of a compound of the formula I (e.g., 2-dimethylaminomethylcyclododecaonone or its salt) as choloretic agent, wherein said compound is administered in dosage range of 625-1250 mg/kg (orally or subcutaneously) or 156-312mg/kg (intravenously) to rat (abstract; page 1, column 1, lines 15-28; Example).

Although Dimmock is silent about the activity of said compound in "inhibiting function and/or proliferation of a cell expressing Janus tyrosine kinase 3" (claims 1 and 4-8), "suppressing an undesired function of a cell expressing Januse tyrosine kinase 3 in mammalian subject" (claims 10-11), "cell division is blocked" (claim 5), "block cell division in said T-cell" (claim 11), "the cell is of lymphoid or myeloid origin" (claim 4), "substantially non-inhibitory of protein tyrosine kinase activity other than Janus tyrosine kinase 3 activity" (claim 6), "inhibiting Jak3 activity at least 3 fold more than inhibiting Jak2 activity in said T-cells" (claim 7) or "less capable of inhibiting Jak2 and Stat5a/b activation by prolactin (PRL) at a concentration sufficient to inhibit Jak3 and Stat5a/b activated by IL2" (claim 8), such characteristic or property must be inherent to the referenced teaching since the administration of same compound in overlapping dosage amount to the mammalian subject (rat) would inherently provide the claimed utility. Thus, the reference anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chimie et Atomistique (FR 1466205 or CA 712187).

The teaching of (FR 1466205 or CA 712187) has been discussed in above 102(b) rejection.

The teaching of FR 1466205 differs from the claimed invention in the continuously or periodically administering of said compound.

However, those of ordinary skill in the art would have been readily optimized effective concurrent administration regimens as determined by good medical practice and the clinical condition of the individual patient. Determination of the appropriate administration regimens for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, absent evidence to the contrary.

Conclusion

12. No Claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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